

Amendments to the Specification:

Please amend the specification as follows:

Please delete the paragraphs on page 3, line 34 to page 4, line 14 and replace them with the following paragraphs:

The present invention also provides (7) soluble HM1.24 antigen protein having the amino acid sequence as set forth in SEQ ID NO: ~~[[1]]~~20.

The present invention also provides (8) a fusion protein of the soluble HM1.24 antigen protein described in the above (7) and another peptide or polypeptide. Specific examples of fusion proteins of soluble HM1.24 antigen protein and another peptide or polypeptide are described in SEQ ID NO: ~~3 and 4~~22 and 23.

The present invention also provides (9) DNA encoding the soluble HM1.24 antigen protein or a fusion protein of the soluble HM1.24 antigen protein and another peptide or polypeptide described in the above (7) and (8). DNA encoding soluble HM1.24 antigen protein or a fusion protein of soluble HM1.24 antigen protein and another peptide or polypeptide has the sequence as set forth in SEQ ID NO: ~~[[1]]~~20. Other specific examples include the nucleotide sequences as set forth in SEQ ID NO: 3 and 4.

Please delete the paragraphs on page 6, line 21 to page 7, line 13 and replace them with the following paragraphs:

Fig. 14 is a drawing that shows the amino acid sequence corresponding to the nucleotide sequence of cDNA encoding HM1.24 antigen protein.

~~Fig. 15 is a drawing that shows the amino acid sequence corresponding to the nucleotide sequence of cDNA encoding HM1.24 antigen protein.~~

Fig. ~~[[16]]~~15 is a schematic diagram showing clone P3.19 isolated by the Panning method and 5 clones (IS1 to IS5) isolated by the immunoscreening method.

Fig. ~~[[17]]~~16 is a drawing that shows the result of flow cytometry analysis using anti-HM1.24 antibody (A: CHO/NEO, B: CHO/HM). The histogram of anti-HM1.24 antibody is shown by a solid line, and that of the control antibody (UPC10) that showed the same isotype is shown by a broken line. In the figure, the abscissa refers to fluorescence intensity and the ordinate to cell count.

Fig. [[18]]17 a photograph in which the expression of HM1.24 antigen in each cell line and CHO cells expressing HM1.24 was detected by the immunoprecipitation/Western blotting method using anti-HM1.24 antibody. After immunoprecipitation using the anti-HM1.24 antibody-bound Sepharose 4B (lanes 1 to 6) or unbound Sepharose 4B (lanes 7 and 8), Western blotting was carried out using anti-HM1.24 antibody to detect HM1.24 antigen (shown on the right). (*: anti-HM1.24 antibody H chain).

Fig. [[19]]18 is a graph showing a standard curve of humanized anti-HM1.24 antibody in the ELISA system that employs GST-tagged soluble HM1.24 antigen expressed by *Escherichia coli*.

Please delete the paragraphs on page 7, line 14 to page 9, line 4 and replace them with the following paragraphs:

The soluble HM1.24 antigen protein of the present invention may be any protein as long as it has the amino acid sequence comprising Asn at amino acid position 1 to Gln at amino acid position 132 of the amino acid sequence as set forth in SEQ ID NO: [[1]]20 and it has the biological activity of soluble HM1.24 antigen protein. The biological activity of soluble HM1.24 antigen protein, as used herein, means that it can be specifically bound to anti-HM1.24 antibody, it is not bound to the cell membrane but is free from it and soluble, and it is a dimer.

The soluble HM1.24 antigen protein of the present invention may also be any soluble HM1.24 antigen protein that has the biological activity of soluble HM1.24 antigen protein, and has the amino acid sequence which has been modified by substitution, deletion and/or addition of one or a plurality of amino acids in the amino acid sequence as set forth in SEQ ID NO: [[1]]20. More specifically, the soluble HM1.24 antigen protein of the present invention may have amino acids in which one or more than one, preferably one or not greater than 24, and more preferably one or not greater than 12 amino acid residues have been substituted in the amino acid sequence as set forth in SEQ ID NO: [[1]]20.

Alternatively, the amino acid sequence as set forth in SEQ ID NO: [[1]]20 may be modified by deletion of one or more than one, preferably one or not greater than 42, and more preferably one or not greater than 17 amino acid residues. Alternatively, the amino acid sequence as set forth in SEQ ID NO: [[1]]20 may be modified by the addition of one or more

than one, preferably one or not greater than 50, and more preferably one or not greater than 14, amino acid residues. The soluble HM1.24 antigen protein for use in the present invention may have undergone modification by the above substitution, deletion, and/or addition at the same time.

Soluble HM1.24 antigen protein has been demonstrated to exhibit its biological activity as long as it has the amino acid sequence comprising amino acid Asn at position 1 to amino acid Arg at position 90 in SEQ ID NO: [[1]]20. The soluble HM1.24 antigen protein of the present invention may be a soluble HM1.24 antigen protein that has the amino acid sequence from amino acid Asn at position 1 to amino acid Arg at position 90 in SEQ ID NO: [[1]]20, or the amino acid sequence modified by the substitution, deletion, and/or addition of one or a plurality of amino acid residues in the amino acid sequence from amino acid Asn at position 1 to amino acid Arg at position 90.

Soluble HM1.24 antigen protein may be a soluble HM1.24 antigen protein that has the amino acid sequence from amino acid Arg at position 90 to amino acid Gln at position 132 in SEQ ID NO: [[1]]20, or the amino acid sequence modified by the substitution, deletion, and/or addition of one or a plurality of amino acid residues to this amino acid sequence, as long as it has the biological activity.

As a soluble HM1.24 antigen protein having the amino acid sequence modified by the substitution, deletion, and/or addition of one or a plurality of amino acid residues in the amino acid sequence of SEQ ID NO: [[1]]20, there may be mentioned a soluble HM1.24 antigen protein having the amino acid sequence as set forth in SEQ ID NOs: ~~3 and~~ 422 and 23.

Please delete the paragraphs on page 10, line 28 to page 11, line 18 and replace them with the following paragraphs:

The amino acid sequence of human HM1.24 antigen protein expressed on the cell membrane is shown in SEQ ID NO: [[16]]26. *E. coli* that has the plasmid pRS38-pUC19 having DNA encoding human protein having an amino acid sequence as set forth in SEQ ID NO: [[16]]26 at the XbaI cleavage site was designated as *Escherichia coli* DH5α (pRS38-pUC19) and has been internationally deposited under the provisions of the Budapest Treaty

on October 5, 1993, with the National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology, of 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki pref., Japan, under accession number FERM BP-4434.

The soluble HM1.24 antigen proteins of the present invention may be the above proteins that are fused to another peptide or polypeptide, as long as they have the biological activity of soluble HM1.24 antigen protein. Such fusion proteins may be produced by a known method. Another peptide or polypeptide subjected to fusion with the protein may be any peptide or polypeptide as long as it can be advantageously used in the present invention. As such peptides, for example, known peptides may be used including FLAG (Hopp, T. P. et al., BioTechnology (1988) 6, 1204-1210), 6 x His comprising 6 His (histidine) residues (**SEQ ID NO: 30**), 10 x His (**SEQ ID NO: 31**), influenza hemagglutinin (HA), fragments of human c-myc, fragments of VSV-GP, fragments of p18HIV, T7-tag, HSV-tag, E-tag, fragments of SV40T antigen, lck tag, fragments of α -tubulin, B-tag, fragments of Protein C, and the like.

Please delete the paragraph on page 39, lines 20-30 and replace it with the following paragraph:

This plasmid DNA was used as a FLAG-tagged soluble antigen expression plasmid and was designated as pSFHM1.24. The sequencing of the nucleotide sequence thereof was carried out using an automatic DNA sequencer (manufactured by Applied Biosystem Inc.) and the Taq Dye Terminator Cycle Sequencing Kit (manufactured by Applied Biosystem Inc.) according to the protocol indicated by the manufacturer. As a result, a structure was confirmed that permits the expression of a fusion protein (SEQ ID NO: **[[2]]21**) in which the soluble antigen is connected to the tag peptide of FLAG.

Please delete the paragraph on page 40, lines 6-10 and replace it with the following paragraph:

The gene encoding the epitope of hemagglutinin (amino acid sequence: YPYDVDPDYA (**SEQ ID NO: 24**)) used was a synthetic DNA pair (manufactured by Scimedia) in which DraIII and KpnI restriction enzyme recognition sites were connected as linkers (SEQ ID NO: 14 and 15).

Please delete the paragraph on page 61, line 8 to page 62, line 4 and replace it with the following paragraph:

The Coating Buffer (CB) used was a 100 mmol/L NaHCO₃ solution containing 0.02% NaN₃, the dilution Buffer (DB) used was a 50 mmol/L Tris-HCl, pH 8.1, solution containing 1 mmol/L MgCl₂, 150 mmol/L NaCl, 0.05% Tween 20, 0.02% NaN₃, and 1% BSA, the substrate Buffer (SB) used was 50 mmol/L NaHCO₃, pH 9.8, solution containing 10 mmol/L MgCl₂, and the 0.1% Tween 20/TBS used was TBS (Takara Code T903, Lot 291) containing 0.1% Tween 20. GST. IS-1 (D) was directly immobilized to the Nunc Immuno Plate Maxi Sorp and the concentration of humanized anti-HM1.24 antibody was determined. GST. IS-1 (D) was diluted with CB and added to the Nunc Immuno Plate Maxi Sorp at 100 µl/well and immobilized at room temperature for 1 hour. After washing three times at 200 µl/well with 0.1% Tween 20/TBS, DB was added at 200 µl/well, to block, at room temperature for more than 1 hour. As a test sample, humanized anti-HM1.24 antibody diluted with DB was reacted at 100 µl/well at room temperature for 1 hour. Then, after washing three times with 0.1% Tween 20/TBS at 200 µl/well, alkaline phosphatase-labeled goat anti-IgG antibody (Goat anti human IgG γ chain AP conjugate) (Biosource AH20305, Lot 6202) was reacted at 100 µl/well at room temperature for 1 hour. After washing three times with 0.1% Tween 20/TBS at 200 µl/well, Sigma 104 diluted prepared at 1 mg/ml with SB was added at 100 µl/well and was allowed to develop color at room temperature for 1 hour. Absorbance at 405 nm-620 nm was determined using the Bio-Rad Model 3550. As a result, an increase in absorbance was obtained, in a dose dependent manner, depending on the concentration of humanized anti-HM1.24 antibody (Figure [[19]]18).

Please delete the paragraphs on page 65, line 27 to page 66, line 13 and replace them with the following paragraphs:

Furthermore, E. coli having the plasmid that contains the DNA (SEQ ID NOS 17-18, respectively, in order of appearance) encoding the a version (SEQ ID NO: [[17]]27) of the L chain V region or the r version (SEQ ID NO: [[18]]28) of the H chain V region of humanized anti-HM1.24 antibody has been internationally deposited under the provisions of the Budapest Treaty as Escherichia coli DH5 α (pUC19-RVLa-AHM-gk) and Escherichia coli

DH5 α (pUC19-RVHr-AHM-gy1), respectively, on August 29, 1996 with the National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology, of 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki pref., Japan, as FERM BP-5645 and FERM BP-5643, respectively.

Furthermore, E. coli having the plasmid that contains the DNA **(SEQ ID NO: 19)** encoding the s version (SEQ ID NO: ~~[[19]]~~**29**) of the H chain V region of humanized anti-HM1.24 antibody has been internationally deposited under the provisions of the Budapest Treaty as Escherichia coli DH5 α (pUC19-RVHs-AHM-gy1) on September 29, 1997 with the National Institute of Bioscience and Human Technology, Agency of Industrial Science and Technology, of 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki pref., Japan, as FERM BP-6127.

Please delete the paragraph on page 68, lines 4-16, and replace it with the following paragraph:

By repeating panning three times using a plasmid library (library A) containing 5 x 10⁵ clones as a starting material, a plasmid DNA having an about 0.9 kbp cDNA as an insert was concentrated. Using Dye Terminator Cycle Sequencing Kit (manufactured by Applied Biosystem Inc.), the nucleotide sequence was determined by the 373A or 377DNA Sequencer (Applied Biosystems). The result revealed that clone P3.19 comprises 1,012 bp cDNA and has an open reading frame (23-549) encoding 180 amino acids (~~Figures 14 and 15~~ **Figure 14**) (SEQ ID NO: 16). The amino acid sequence deduced from the cDNA had a structure characteristic to type II membrane proteins and had 2 N-type sugar chain binding sites.

Please delete the paragraph on page 69, lines 3-12, and replace it with the following paragraph:

By immunoscreening, five positive clones were isolated, all of which were consistent with the partial sequence of P3.19 (Figure ~~[[16]]~~**15**). Homology search of them revealed that P3.19 is identical with the nucleotide sequence of BST-2 (Ishikawa J. et al., Genomics, 26: 527-534, 1995) expressed on the bone marrow or synovial stromal cells. The same molecule was obtained from two runs of immunoscreening, which strongly suggested that membrane protein encoded by P3.19 is the HM1.24 antigen molecule.

Please delete the paragraph on page 70, lines 6-12, and replace it with the following paragraph:

As result of FACS analysis, CHO cells in which P3.19 has been introduced were shown to react strongly with anti-HM1.24 antibody, whereas no binding was obtained in CHO cells (CHO/NEO) in which the control expression vector has only been introduced (Figure [[17]]16). It was confirmed therefore that the protein encoded by P3.19 binds to anti-HM1.24 antibody.

Please delete the paragraph on page 70, line 27 to page 71, line 1 and replace it with the following paragraph:

Each of myeloma cell lines KPMM2, RPMI8226, and U266 strongly expressed HM1.24 antigen, and immunoprecipitation of the cell lysates thereof with anti-HM1.24 antibody allowed the specific detection of proteins having a molecular weight of about 29-33 kDa (Figure [[18]]17). In a similar experiment for CHO cell lines (CHO/HM) in which P3.19 has been introduced, immunoprecipitants were confirmed in the CHO/HM cells as for the myeloma cell lines (Figure [[18]]17, lane 4). Such immunoprecipitants could not be confirmed in the control cells (CHO/NEO) in which the expression vector pCOS1 has only been introduced (Figure [[18]]17, lane 5).

Please delete the paragraphs on page 71, line 11 to page 72, line 9 and replace them with the following paragraphs:

SEQ ID NO: 1 shows the amino acid sequence **(SEQ ID NO: 20)** and the nucleotide sequence of the extracellular domain of soluble HM1.24 antigen protein.

SEQ ID NO: 2 shows the amino acid sequence **(SEQ ID NO: 21)** and the nucleotide sequence of a fusion protein comprising the leader sequence, the FLAG peptide and soluble HM1.24 antigen protein. A sequence comprising Met at position 1 to His at position 18 represents the leader sequence. A sequence comprising Asp at position 20 to Lys at position 27 represents the FLAG peptide. A sequence comprising Gly at position 28 to Thr at position 29 is a linker.

SEQ ID NO: 3 shows the amino acid sequence **(SEQ ID NO: 22)** and the nucleotide sequence of a fusion protein comprising the HA peptide and the soluble HM1.24 antigen

protein. A sequence comprising Tyr at position 1 to Ala at position 9 represents the HA peptide. A sequence comprising Gly at position 28 to Thr at position 29 is a linker.

SEQ ID NO: 4 shows the amino acid sequence (SEQ ID NO: 23) and the nucleotide sequence of a fusion protein comprising the HA peptide and the C-terminal-deleted soluble HM1.24 antigen protein. A sequence comprising Tyr at position 1 to Ala at position 9 represents the HA peptide. A sequence comprising Gly at position 28 to Thr at position 29 is a linker.

SEQ ID NO: 5 shows the nucleotide sequence of the determined CGM/HA and the amino acid sequence (SEQ ID NO: 24) of the HA peptide. A sequence comprising Tyr at position 1 to Ala at position 9 represents the HA peptide.

SEQ ID NO: 6 shows the amino acid sequence (SEQ ID NO: 25) and the nucleotide sequence of the determined CGM/HA-HM164. A sequence comprising Met at position 1 to Cys at position 20 represents a leader sequence. A sequence comprising Gly at position 3 to Thr at position 32 is a linker. A sequence comprising Asn at position 33 to Ala at position 151 is the C-terminal-deleted soluble HM1.24 antigen protein.

Please delete the paragraphs on page 72, line 31 to page 73, line 5 and replace them with the following paragraphs:

SEQ ID NO: 16 shows the amino acid sequence (SEQ ID NO: 26) and the nucleotide sequence of human HM1.24 antigen protein expressed on the cell membrane.

SEQ ID NO: 17 shows the amino acid sequence (SEQ ID NO: 27) and the nucleotide sequence of the a version of the L chain V region of humanized anti-HM1.24 antibody.

SEQ ID NO: 18 shows the amino acid sequence (SEQ ID NO: 28) and the nucleotide sequence of the r version of the H chain V region of humanized anti-HM1.24 antibody.

SEQ ID NO: 19 shows the amino acid sequence (SEQ ID NO: 29) and the nucleotide sequence of the s version of the H chain V region of humanized anti-HM1.24 antibody.